Bioorganic & Medicinal Chemistry Letters 22 (2012) 5063–5066

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

$InCl_3$-catalysed synthesis of 2-aryl quinazolin-4(3*H*)-ones and 5-aryl pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones and their evaluation as potential anticancer agents

Naveen Mulakayala [a,*], Bhaskar Kandagatla [a], Ismail [a], Rajesh Kumar Rapolu [a], Pallavi Rao [a], Chaitanya Mulakayala [b], Chitta Suresh Kumar [b], Javed Iqbal [a], Srinivas Oruganti [a,*]

[a] Cosmic Discoveries, Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500046, India
[b] Department of Biochemistry, Sri Krishnadevaraya University, Anatapur 515003, India

ARTICLE INFO

Article history:
Received 26 April 2012
Revised 22 May 2012
Accepted 1 June 2012
Available online 13 June 2012

Keywords:
2-Aryl quinazoline-4(3*H*)-one
2-Aminobenzamides
$InCl_3$
5-Aryl pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones
antitumor activity

ABSTRACT

A convenient and practical methodology for the synthesis of 2-aryl quinazolin-4(3*H*)-ones by the condensation of *o*-aminobenzamides with aromatic aldehydes under mild conditions using catalytic $InCl_3$ with good yields and high selectivities. This method has been extended for the synthesis of 5-aryl pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones which have potential applications in medicinal chemistry. Many of these compounds were evaluated for their anti-proliferative properties in vitro against four cancer cell lines and several compounds were found to be active. Further in vitro studies indicated that inhibition of sirtuins could be the possible mechanism of action of these molecules.

Quinazolinones occur widely in nature and exhibit a wide range of biological activities viz. epidermal growth factor (EGF) receptors of tyrosine kinase,[1] anticancer,[2] antiviral,[3] anti-tubercular agents,[4] treatment of diabetes and obesity,[5] anti-inflammatory,[6] insecticidal and anti-microbial activity.[7] Quinazolin-4(3*H*)-ones are used as ligands for benzodiazepine and AMPA receptors in the CNS system[8] or as DNA binders.[9] Naturally occurring alkaloids such as luotonin A **1** from *Peganum nigellastrum*,[10a] 2-methyl-4(3*H*)-quinazolinone **2** from *Bacillus cereus*,[10b] 2-(4-hydroxybutyl) quinazolin-4-one **3** from *Dichroa febrifuga*,[10c] bouchardatine **4** from *Bouchardatia neurococca*[10d] and EGFR Tyrosine Kinase inhibitors (cellular trans-membrane tyrosine kinases that is over-expressed in a significant number of human tumors) that is PD 153035 **5** and Gefitinib **6**[10e] have Quinazolinone skeleton (Fig. 1).

In the last decade, several methods have been reported for the syntheses of quinazoline[11] and quinazolinone derivatives.[12–14] However, most of the methods requires higher temperatures for the condensation, which may preclude the presence of sensitive functionalities. We were interested in identifying mild reaction conditions for the construction of substituted quinazolinone derivative structurally present in complex alkaloids with multiple functionalities.

Our interest in the use of Lewis acids for the construction of various heterocyclic motifs, prompted us to study the quinazolinone cyclization using various Lewis acids. In particular, $InCl_3$ has emerged as a mild Lewis acid catalyst for a variety of organic transformations.[15–23] Compared to conventional Lewis acids, $InCl_3$ has advantages of higher stability in water, operational simplicity, strong tolerance to oxygen and nitrogen containing substances and functional groups and it can often be employed in catalytic amounts.

Our initial effort was the cyclic condensation of *o*-aminobenzamide **7** with various aromatic aldehydes **8** as model substrates for the preparation of 2-aryl quinazolin-4(3*H*)-ones **9** (Scheme 1). We were delighted to find that *o*-aminobenzamide reacted with aromatic aldehydes in the presence of 10 mol % of $InCl_3$ to furnish 2-arylquinazolin-4(3*H*)-ones **9a–g**[24] in good to excellent isolated yields (Table 1).

In the absence of $InCl_3$, the condensation of *o*-aminobenzamide and aromatic aldehyde did not proceed neither at room temperature nor at reflux temperature. We presume that the presence of $InCl_3$ promotes the cyclisation via an imine intermediate.

In our efforts to optimize the reaction conditions, we studied the formation of **9a** and have observed that yields were higher in acetonitrile as compared to other solvents (Table 2). Reduction in the amount of $InCl_3$ from 10 to 1 mol % produced cyclized product **9a** in diminished yields. This suggests that the use of 5–10 mol % $InCl_3$ in acetonitrile is critical to obtain the products in good yields.

* Corresponding authors. Tel.: +91 40 665 71626; fax: +91 40 665 71158 (N.M.).
E-mail addresses: naveen071280@gmail.com, naveenm@ilsresearch.org (N. Mulakayala).

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.06.003

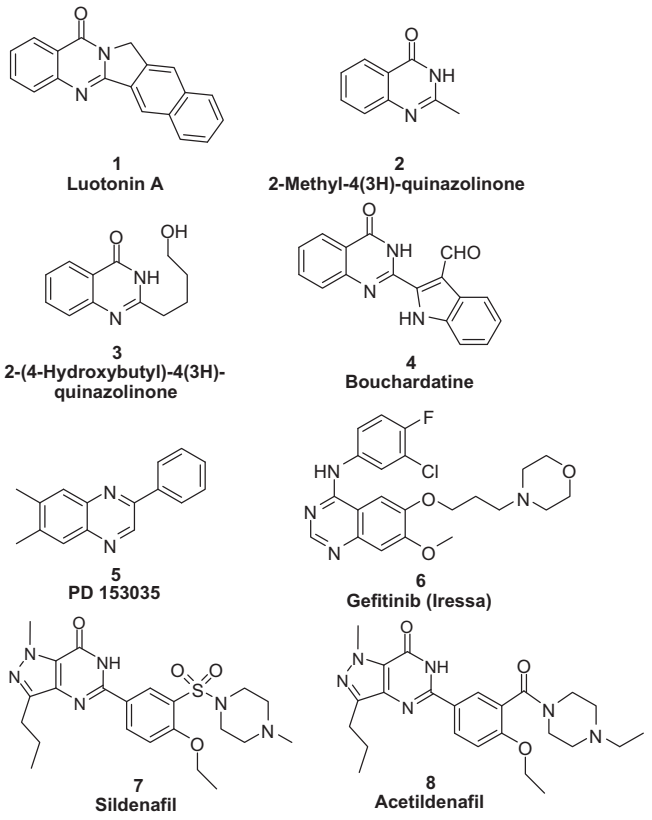
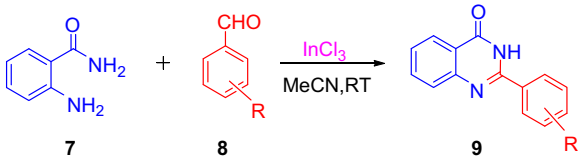


Figure 1. Bioactive compounds containing quinazolin-4(3*H*)-one and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one skeleton.



Scheme 1. $InCl_3$-catalyzed reaction between *o*-amino-benzamide and aromatic aldehyde.

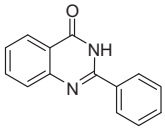
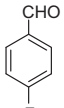
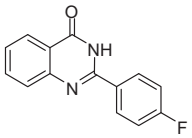
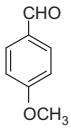
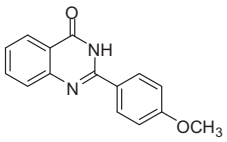
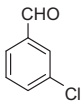
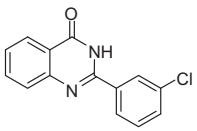
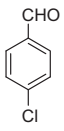
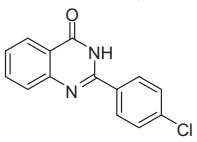
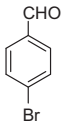
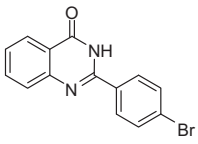
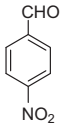
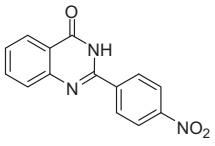
The catalytic activity of $InCl_3$ in the synthesis of 2-aryl quinazolin-4(3*H*)-ones prompted us to investigate its application for the synthesis of other therapeutically relevant scaffolds. In this regard, we employed the $InCl_3$ methodology for the construction of 5-aryl pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one systems which are the key structural motifs of important drugs like Sildenafil **5** and acetildenafil **6** (Fig. 1).

The catalytic activity of other Lewis acids like $AlCl_3$, $TiCl_4$, BF_3-OEt_2, $FeCl_3$, $CuCl_2$ in the synthesis of 2-aryl quinazolin-4(3*H*)-ones give moderate yields of the desired product (Table 3).

We observed that 4-amino-1-methyl-3-propylpyrazole-5-carboxamide[25] reacted with aromatic aldehydes in the presence of 10 mol % of $InCl_3$ at room temperature to furnish 5-aryl pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones **11a–h**[24] (Scheme 2) in good to excellent isolated yields (Table 4).

Having the optimized reaction condition for the preparation of 5-aryl pyrazolo [4,3-*d*]pyrimidin-7(6*H*)-ones and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones in hand we then examined the generality and scope of this methodology. Thus a variety of aromatic aldehydes **8** were reacted with amino benzamide **7** and substituted pyrazole-5-carboxamide **10** in MeCN at room temperature using $InCl_3$ and results are presented in Tables 1–3. The reaction proceeded well in all these cases and the substituents like F, Cl, Br, OMe, Me, NO_2 and $-OCHF_2$ present in the aromatic aldehydes **8** were well tolerated. The reaction appeared to be clean as no formation of side product was observed and the desired product **9** & **11** were isolated in good to excellent yield in each case. All the compounds synthesized were well characterized by spectral (NMR, MS and IR) data.

Table 1
$InCl_3$-catalyzed synthesis of 2-aryl quinazolin-4(3*H*)-one derivatives

Compound	Aldehyde	Product	Time (min)	Yield[a] (%)
9a			30	88
9b			45	94
9c			60	87
9d			40	92
9e			45	92
9f			45	92
9g			60	88

[a] Isolated yield.

Table 2
Optimisation of $InCl_3$-catalyzed reaction of 2-phenyl quinazolin-4(3*H*)-one **9a**

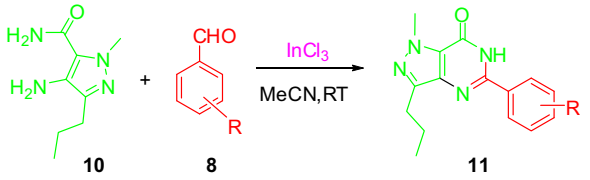
Entry	Mol % of $InCl_3$	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	10	CH_3CN	rt	0.5	92
2	5	CH_3CN	rt	1	88
3	10	MeOH	rt	2	86
4	5	MeOH	rt	4	84
5	10	CH_2Cl_2	rt	6	67
6	10	$CHCl_3$	rt	9	65
8	10	iPrOH	rt	12	62
7	10	EtOAc	rt	18	60

[a] Isolated yield.

Table 3
Optimisation of the catalyst for the preparation of 2-phenyl quinazolin-4(3*H*)-one **9a**

Entry	Mol %	Lewis acid	Temp (°C)	Time (h)	Yield[a] (%)
1	10	$InCl_3$	rt	0.5	92
2	5	$InCl_3$	rt	1	88
3	10	$AlCl_3$	rt	4	66
4	10	$AlCl_3$	60	4	70
5	10	$TiCl_4$	rt	6	53
6	10	$FeCl_3$	rt	6	50
8	10	$BF_3.OEt_2$	rt	6	54
7	10	$CuCl_2$	rt	6	45

[a] Isolated yield.

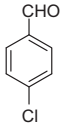
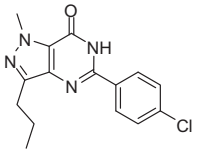
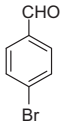
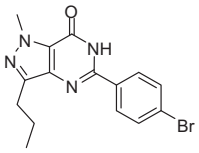
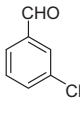
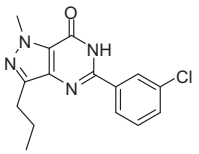
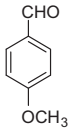
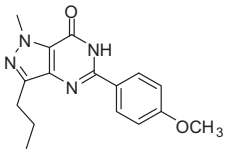
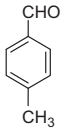
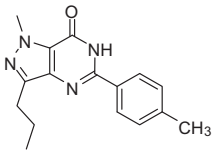
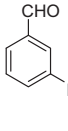
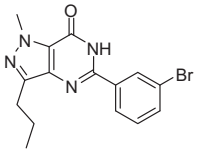
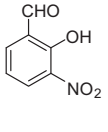
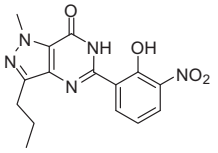
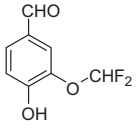
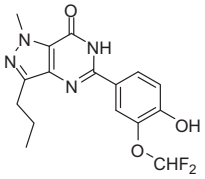


Scheme 2. $InCl_3$-catalyzed synthesis of 5-aryl pyrazolo [4,3-*d*]pyrimidin -7(6*H*)-ones.

Based on the precedence of known anticancer activity of known quinazolin-4(3*H*)-one[10e] derivatives we were interested to test anticancer properties in vitro. We evaluated our compounds for their anti-proliferative properties in vitro against a number of cancer cell lines for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and human breast cancer cell line (MDA-Mb 231MR32). The test compounds were examined at various concentrations in a MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay and the IC_{50} values obtained for each compounds are summarized in Table 5. Harmine, a member of β-carboline family of compounds showed cytotoxicity against HL60 and K562 cell lines[26] was used as a reference compound. While most of these compounds showed inhibition of leukemia cell growth as reflected by their IC_{50} values the good results however were obtained using compounds **9b**, **9d**,**11a**, **11b**, **11c**, **11h** (IC_{50} <19 μM, Table 5). Interestingly, except compounds **9e** and **11b** all other compounds (IC_{50} <20 μM, Table 5) were found to be active against colon carcinoma cells and except compounds **9a**, **9d**, **9f**, **11a**, **11b**, **11e** and **11g** rest of the compounds (IC_{50} <45 μM, Table 5) showed good activities against breast cancer cells. Overall, compound **11h** possessing a 4-hydroxy-3-difluoromethoxy phenyl group at C-5 position was found to be promising (IC_{50} ~7–25 μM, Table 5).

In order to understand the mechanism of action some of the compounds were tested for their inhibitory potential against sirtuins. Being considered as important targets for cancer therapeutics sirtuins (class III NAD-dependent deacetylases) are shown to up-regulated in various types of cancer.[27] Inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. The activity of test compounds was determined using Sirt1 fluorescence activity assay using suramin, a known inhibitor of Sirt1 as a reference compound. At the concentration of 10 μM compounds **9b**, **11f**, **11g** and **11h** showed 48%, 59%, 61%, and 63% inhibition, respectively, in compared to suramin's 79% inhibition indicating that the anticancer properties of these molecules are possibly due to their sirtuin inhibiting properties. To understand the nature of interactions between these compounds and the Sir1 protein a molecular docking simulation study was carried out using a representative compound **11h** (Fig. 2). The three dimensional model of hSirt1 (NCBI gi no: 7555471, 200–500 amino acid residues) was developed by homology modeling using the templates PDB: 2HJH and PDB: 1J8F in the Modeller9v6. Nine

Table 4
$InCl_3$-catalyzed synthesis of pyrazolo[4,3-*d*] pyrimidin-7(6*H*)-ones

Compound	Aldehyde	Product	Time (min)	Yield[a] (%)
11a			40	90
11b			45	92
11c			45	90
11d			50	92
11e			40	91
11f			45	94
11g			65	91
11h			75	88

[a] Isolated yield.

amino acid residues, for example, Gly261, Ala262, Ile270, Pro271, Phe273, Arg274, Gln345, Ile347, and His363 were found to play key roles in this interaction with the overall binding energy of −9.6 Kcal/mol indicating that molecule **11h** interacts well with this protein.

In summary, we have developed a convenient methodology for the synthesis of 2-aryl quinazolinone derivatives in high yields via the cyclisation of *o*-aminobenzamide with aromatic aldehydes using $InCl_3$ catalyst. This novel approach for the synthesis of 2-aryl quinazolin-4(3*H*)-ones and 5-aryl pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones is convenient, mild, cost-effective and practically free of chromatographic separation.

General experimental procedure:To a solution of aromatic aldehyde (1.0 mmol) in acetonitrile, *o*-aminobenzamide (1.0 mmol)

Table 5
In vitro cytotoxic activity of the synthesized compounds **9a–f** and **11a–h** against leukemiacells, K562, humancolon carcinoma cells, Colo-205, human breast cancer cell line (MDA-Mb 231MR32)

Compound	IC_{50}[a,b] (μM)		
	K562	Colo-205	MDA-MB 231
9a	19	13	52
9b	17	10	20
9c	24	8	28
9d	18	12	41
9e	20	23	37
9f	21	11	41
9g	19	12	42
11a	15	10	51
11b	17	25	46
11c	16	11	40
11d	21	9	44
11e	19	14	48
11f	24	12	38
11g	21	10	44
11h	15	7	25
Harmine	14	8	32

[a] IC_{50} represent the concentration of compound that causes a 50% growth inhibition to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.

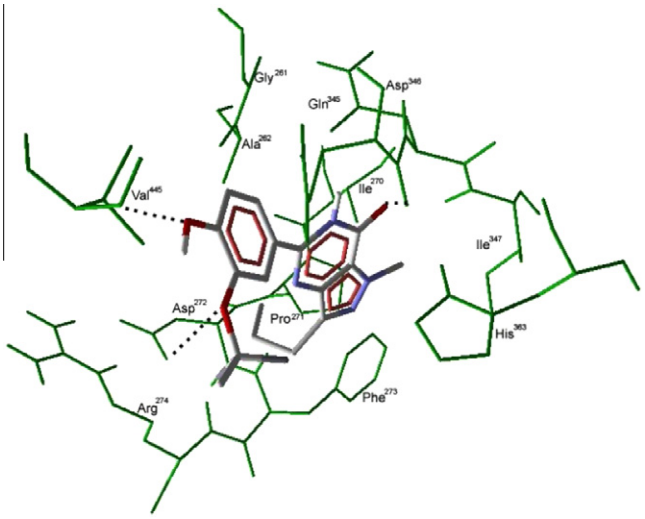


Figure 2. Docking of compound **5b** into the active site of hSirt1.

and $InCl_3$ (10 mol %) were added at room temperature and the reaction mixture was stirred till the completion of the starting materials (indicated by TLC). After filtration through celite, the solvent was evaporated under reduced pressure and the crude product was triturated with 10% diethyl ether in hexane to obtain the pure product. All the compounds isolated were characterized by ^{1}H NMR, ^{13} C NMR and Mass.

Acknowledgement

N.M. and C.M. thanks CSIR, New Delhi, for the award of fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.06.003.

References and notes

1. Ple, P. A.; Green, T. P.; Hennequin, L. F.; Curwen, J.; Fennell, M.; Allen, J.; Lambert-vander Brempt, C.; Costello, G. *J. Med. Chem.* **2004**, *47*, 871.
2. (a) Doyle, L. A.; Ross, D. D. *Oncogene* **2003**, *22*, 7340; (b) Henderson, E. A.; Bavetsias, V.; Theti, D. S.; Wilson, S. C.; Clauss, R.; Jackman, A. L. *Bioorg. Med. Chem.* **2006**, *14*, 5020.
3. (a) Chien, T.-C.; Chen, C.-S.; Yu, F.-H.; Chern, J.-W. *Chem. Pharm. Bull.* **2004**, *52*, 1422; (b) Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. *Antimicrob. Agents Chemother.* **2004**, *48*, 4154.
4. (a) Waisser, K.; Gregor, J.; Dostal, H.; Kunes, J.; Kubicova, L.; Klimesova, V.; Kaustova, J. *Farmaco* **2001**, *56*, 803; (b) Kunes, J.; Bazant, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. *Farmaco* **2000**, *55*, 725.
5. Rudolph, J.; Esler, W. P.; O'Connor, S.; Coish, P. D. G.; Wickens, P. L.; Brands, M.; Bierer, D. E.; Bloomquist, B. T.; Bondar, G.; Chen, L.; Chuang, C.-Y.; Claus, T. H.; Fathi, Z.; Fu, W.; Khire, U. R.; Kristie, J. A.; Liu, X.-G.; Lowe, D. B.; McClure, A. C.; Michels, M.; Ortiz, A. A.; Ramsden, P. D.; Schoenleber, R. W.; Shelekhin, T. E.; Vakalopoulos, A.; Tang, W.; Wang, L.; Yi, L.; Gardell, S. J.; Livingston, J. N.; Sweet, L. J.; Bullock, W. H. *J. Med. Chem.* **2007**, *50*, 5202.
6. Yadav, M. R.; Shirude, S. T.; Parmar, A.; Balaraman, R.; Giridhar, R. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2006**, 1198.
7. Singh, T.; Srivastava, S. S. V. K.; Kumar, A. *Indian J. Chem. B: Org. Med. Chem.* **2006**, *45*, 2558.
8. Arora, D.; Kumar, H.; Malhotra, D.; Malhotra, M. *Pharmacologyonline* **2011**, *3*, 659.
9. Malecki, N.; Carato, P.; Rigo, G.; Goossens, J. F.; Houssin, R.; Bailly, C.; Henichart, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 641.
10. (a) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541; (b) Yoshida, S.; Aoyagi, T.; Harada, S.; Matsuda, N.; Ikeda, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 111; (c) Deng, Y.; Xu, R.; Ye, Y. J. *Chin. Pharm. Sci.* **2000**, *9*, 116; (d) Wattanapiromsakul, C.; Forsterand, P. I.; Waterman, P. G. *Phytochemistry* **2003**, *64*, 609; (e) Noolvi, M. N.; Patel, H. M.; Bhardwaj, V.; Chauhan, A. *Eur. J. Med. Chem.* **2011**, *46*, 2327.
11. (a) Shreder, K. R.; Wong, M. S.; Nomanbhoy, T.; Leventhal, P. S.; Fuller, S. R. *Org. Lett.* **2004**, *6*, 3715; (b) Yoon, D. S.; Han, Y.; Stark, T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775; (c) Costa, M.; Ca, N. D.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469.
12. (a) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659; (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
13. (a) Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6517; (b) Larksarp, C.; Alper, H. *J. Org. Chem.* **2000**, *65*, 2773.
14. (a) Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339; (b) Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363; (c) Subba Reddy, B. V.; Venkateswarlu, A.; Madan, C.; Vinu, A. *Tetrahedron Lett.* **1891**, *2011*, 52.
15. Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149.
16. Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16.
17. Ghosh, R. *Indian J. Chem.* **2001**, *40B*, 550.
18. Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209.
19. Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 3959.
20. Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2008**, *49*, 7139.
21. Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Narasimhulu, G.; Portier, Y.; Madhavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, *49*, 3341.
22. Kumar, R.; Nandi, G. C.; Verma, R. K.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 442.
23. (a) Yadav, J. S.; Sunny, A.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8063; (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M. *Synlett* **2001**, 1781; (c) Yadav, J. S.; Reddy, B. V. S.; Sabitha, G.; Prabhakar, A.; Kunwar, A. C. *Tetrahedron Lett.* **2003**, *44*, 2221; (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, C. S. *Tetrahedron Lett.* **2004**, *45*, 4583; (e) Yadav, J. S.; Reddy, B. V. S.; Madan, C. *New J. Chem.* **2000**, *24*, 853.
24. *Analytical data of selected compounds*: Compound **9a**: mp 237–238 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.6 (br, 1H), 8.18–8.00 (m, 3H), 7.85–7.39 (series of m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7, 152.8, 149.0, 135.0, 133.0, 131.8, 129.0, 128.2, 127.7, 127.0, 126.3, 121.3; Mass (ESI): m/z = 222 $[M+H]^+$; Compound **11h**: mp 276–278 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO d_6): δ 11.56 (br s, 1H), 9.48 (s, 1H), 7.74 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.70 (t, J = 75.6 Hz, 1H), 4.25 (s, 3H), 2.88 (t, J = 7.2 Hz, 2H), 1.84 (q, J = 7.2, 14.0 Hz, 2H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$+DMSO d_6, 100 Hz): δ 155.1, 149.3, 148.7, 146.0, 140.7, 138.2, 131.1, 124.5, 121.8, 118.9, 116.3, 113.3, 38.0, 27.5, 22.1, 13.9; Mass (ESI): m/z = 349.1 $[M-H]^+$.
25. Haning, H.; Niewohner, U.; Schenke, T.; Lampe, T.; Hillisch, A.; Bischoff, E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3900.
26. (a) Jahaniani, F.; Ebrahimi, S. A.; Rahbar-Roshandel, N.; Mahmoudian, M. *Phytochemistry* **2005**, *66*, 1581; (b) Michan, S.; Sinclair, D. *Biochem. J.* **2007**, *404*, 1; (c) Sauve, A. A.; Wolberger, C.; Schramm, V. L.; Boeke, J. D. *Annu. Rev. Biochem.* **2006**, *75*, 435; (d) Saunders, L. R.; Verdin, E. *Oncogene* **2007**, *26*, 5489; (e) Fraga, M. F.; Agrelo, R.; Esteller, M. *Ann. N.Y. Acad. Sci.* **2007**, *60*, 1100; (f) Zhao, W.; Kruse, J. P.; Tang, Y.; Jung, S. Y.; Qin, J.; Gu, W. *Nature* **2008**, *451*, 587.
27. Milne, J. C.; Lambert, P. D.; Schenk, S.; Carney, D. P.; Smith, J. J.; Gagne, D. J.; Jin, L.; Boss, O.; Perni, R. B.; Vu, C. B.; Bemis, J. E.; Xie, R.; Disch, J. S.; Ng, P. Y.; Nunes, J. J.; Lynch, A. V.; Yang, H.; Galonek, H.; Israelian, K.; Choy, W.; Iffland, A.; Lavu, S.; Medvedik, O.; Sinclair, D. A.; Olefsky, J. M.; Jirousek, M. R.; Elliott, P. J. *Nature* **2007**, *450*, 712.